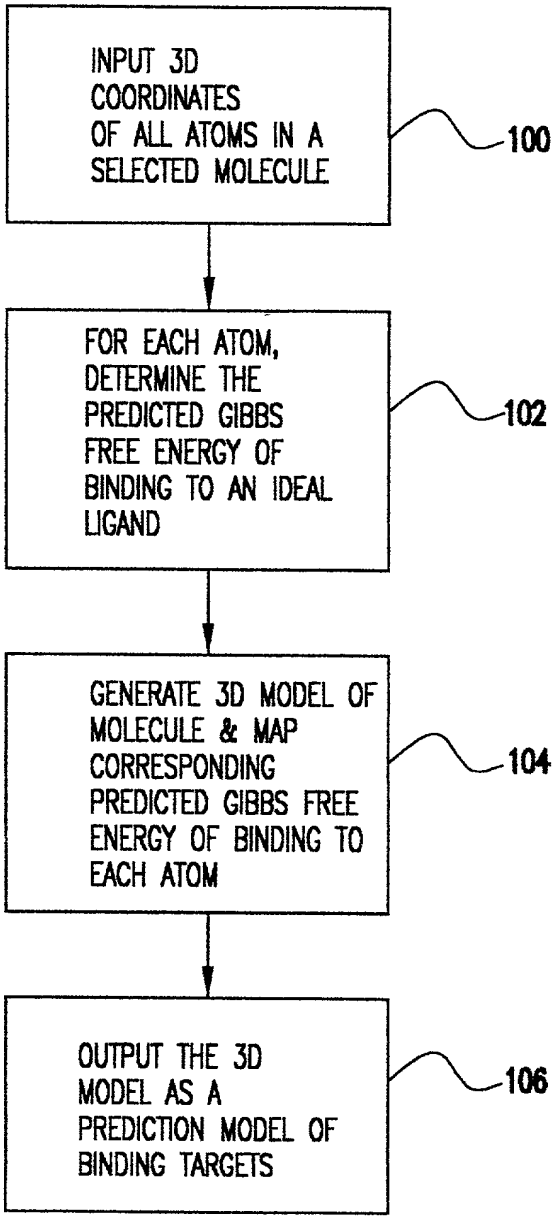

INPUT 3D COORDINATES OF ALL ATOMS IN A SELECTED MOLECULE
100
FOR EACH ATOM, DETERMINE THE PREDICTED GIBBS FREE ENERGY OF BINDING TO AN IDEAL LIGAND
102
GENERATE 3D MODEL OF MOLECULE & MAP CORRESPONDING PREDICTED GIBBS FREE ENERGY OF BINDING TO EACH ATOM
104
OUTPUT THE 3D MODEL AS A PREDICTION MODEL OF BINDING TARGETS
106

FIG.1

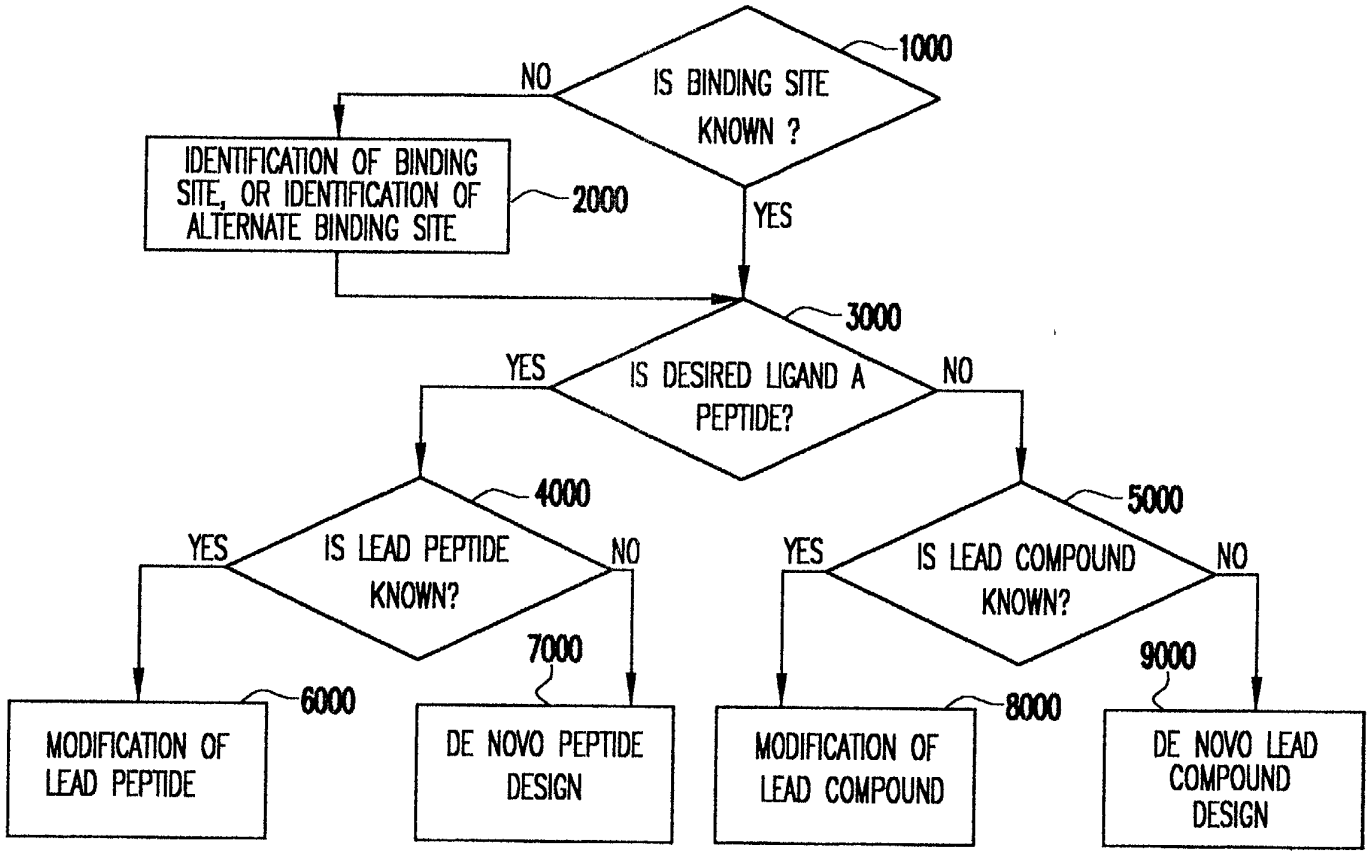


FIG.2

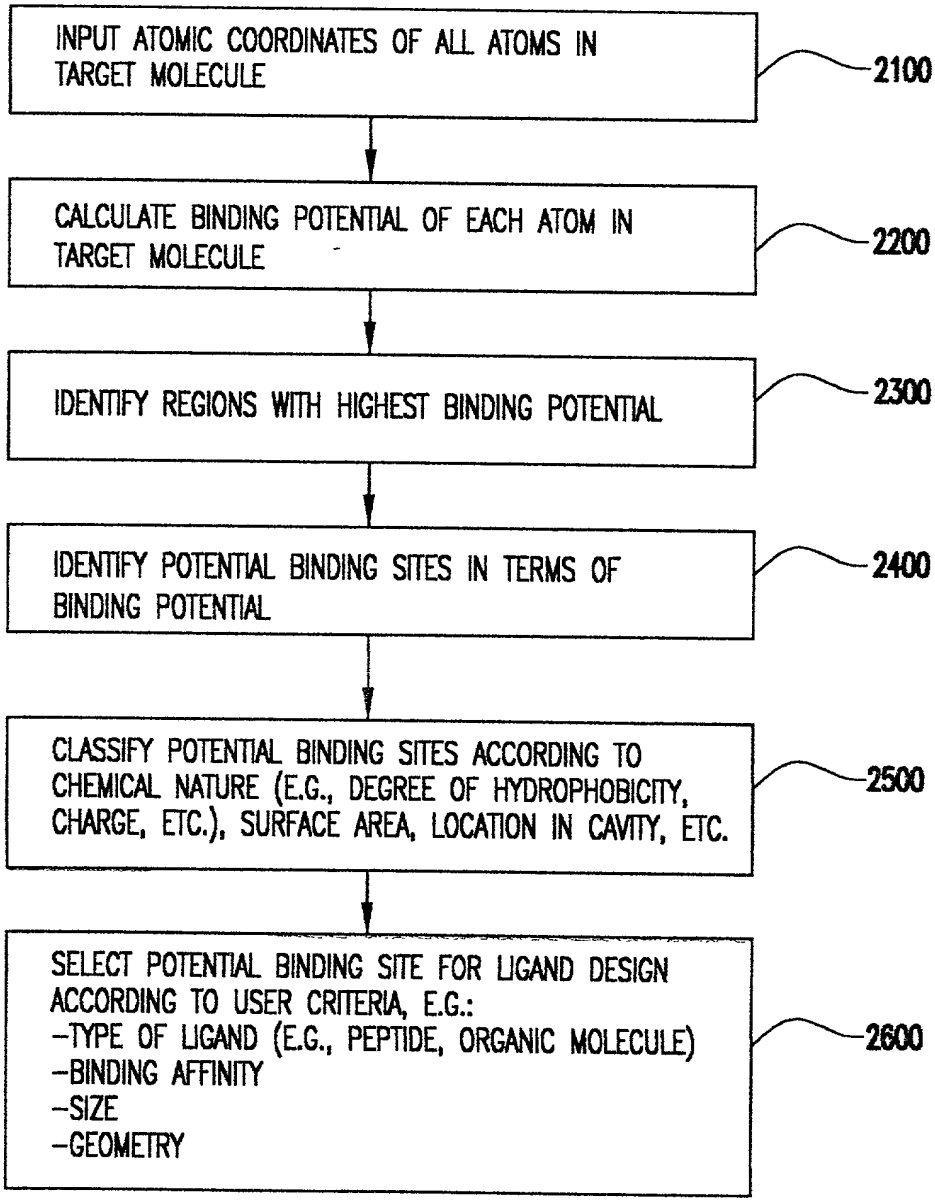

INPUT ATOMIC COORDINATES OF ALL ATOMS IN TARGET MOLECULE
2100
CALCULATE BINDING POTENTIAL OF EACH ATOM IN TARGET MOLECULE
2200
IDENTIFY REGIONS WITH HIGHEST BINDING POTENTIAL
2300
IDENTIFY POTENTIAL BINDING SITES IN TERMS OF BINDING POTENTIAL
2400
CLASSIFY POTENTIAL BINDING SITES ACCORDING TO CHEMICAL NATURE (E.G., DEGREE OF HYDROPHOBICITY, CHARGE, ETC.), SURFACE AREA, LOCATION IN CAVITY, ETC.
2500
SELECT POTENTIAL BINDING SITE FOR LIGAND DESIGN ACCORDING TO USER CRITERIA, E.G.:
-TYPE OF LIGAND (E.G., PEPTIDE, ORGANIC MOLECULE)
-BINDING AFFINITY
-SIZE
-GEOMETRY
2600

FIG.3

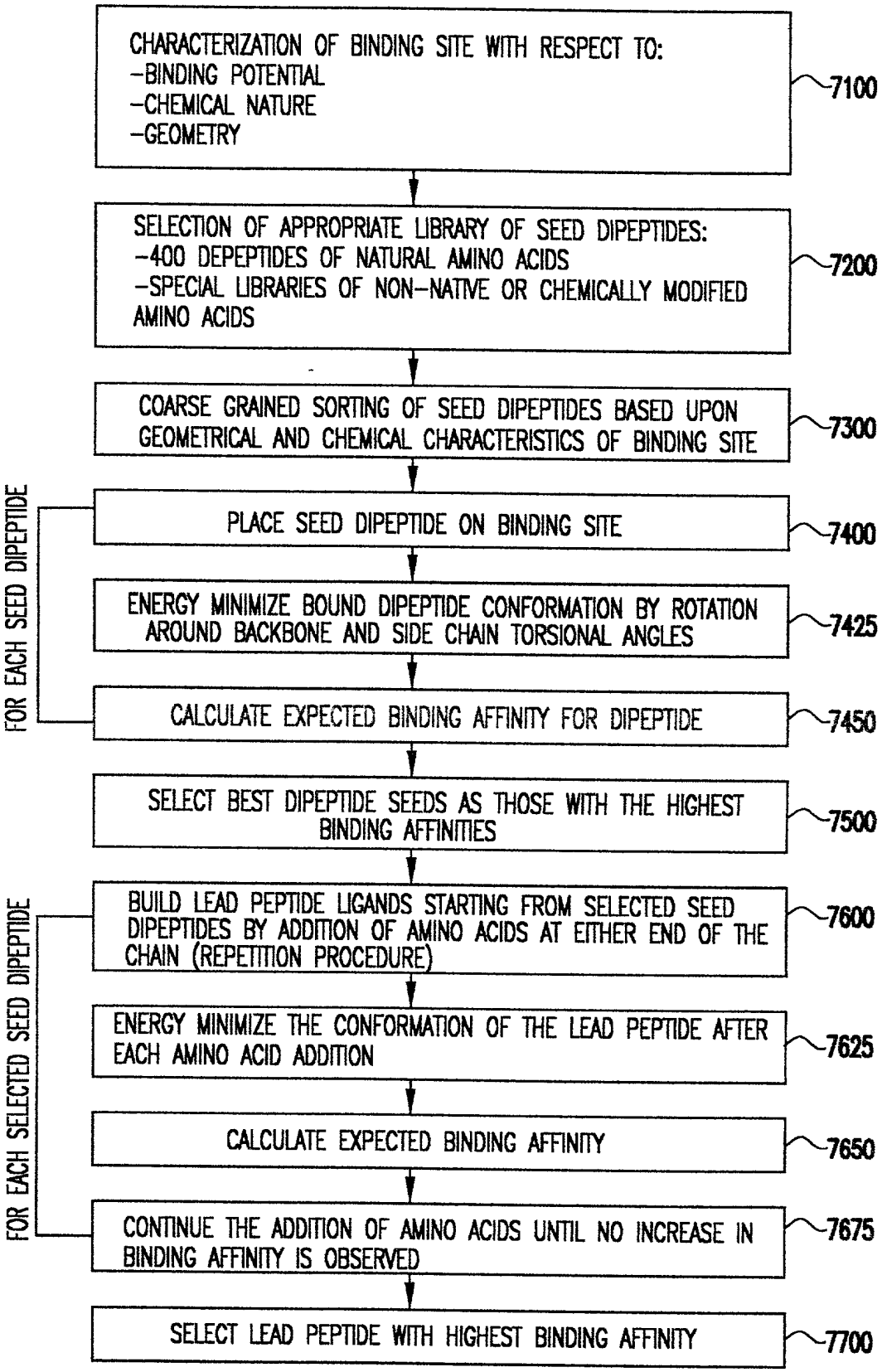

CHARACTERIZATION OF BINDING SITE WITH RESPECT TO:
-BINDING POTENTIAL
-CHEMICAL NATURE
-GEOMETRY
7100
SELECTION OF APPROPRIATE LIBRARY OF SEED DIPEPTIDES:
-400 DEPEPTIDES OF NATURAL AMINO ACIDS
-SPECIAL LIBRARIES OF NON-NATIVE OR CHEMICALLY MODIFIED AMINO ACIDS
7200
COARSE GRAINED SORTING OF SEED DIPEPTIDES BASED UPON GEOMETRICAL AND CHEMICAL CHARACTERISTICS OF BINDING SITE
7300
FOR EACH SEED DIPEPTIDE
PLACE SEED DIPEPTIDE ON BINDING SITE
7400
ENERGY MINIMIZE BOUND DIPEPTIDE CONFORMATION BY ROTATION AROUND BACKBONE AND SIDE CHAIN TORSIONAL ANGLES
7425
CALCULATE EXPECTED BINDING AFFINITY FOR DIPEPTIDE
7450
SELECT BEST DIPEPTIDE SEEDS AS THOSE WITH THE HIGHEST BINDING AFFINITIES
7500
FOR EACH SELECTED SEED DIPEPTIDE
BUILD LEAD PEPTIDE LIGANDS STARTING FROM SELECTED SEED DIPEPTIDES BY ADDITION OF AMINO ACIDS AT EITHER END OF THE CHAIN (REPETITION PROCEDURE)
7600
ENERGY MINIMIZE THE CONFORMATION OF THE LEAD PEPTIDE AFTER EACH AMINO ACID ADDITION
7625
CALCULATE EXPECTED BINDING AFFINITY
7650
CONTINUE THE ADDITION OF AMINO ACIDS UNTIL NO INCREASE IN BINDING AFFINITY IS OBSERVED
7675
SELECT LEAD PEPTIDE WITH HIGHEST BINDING AFFINITY
7700

FIG.4

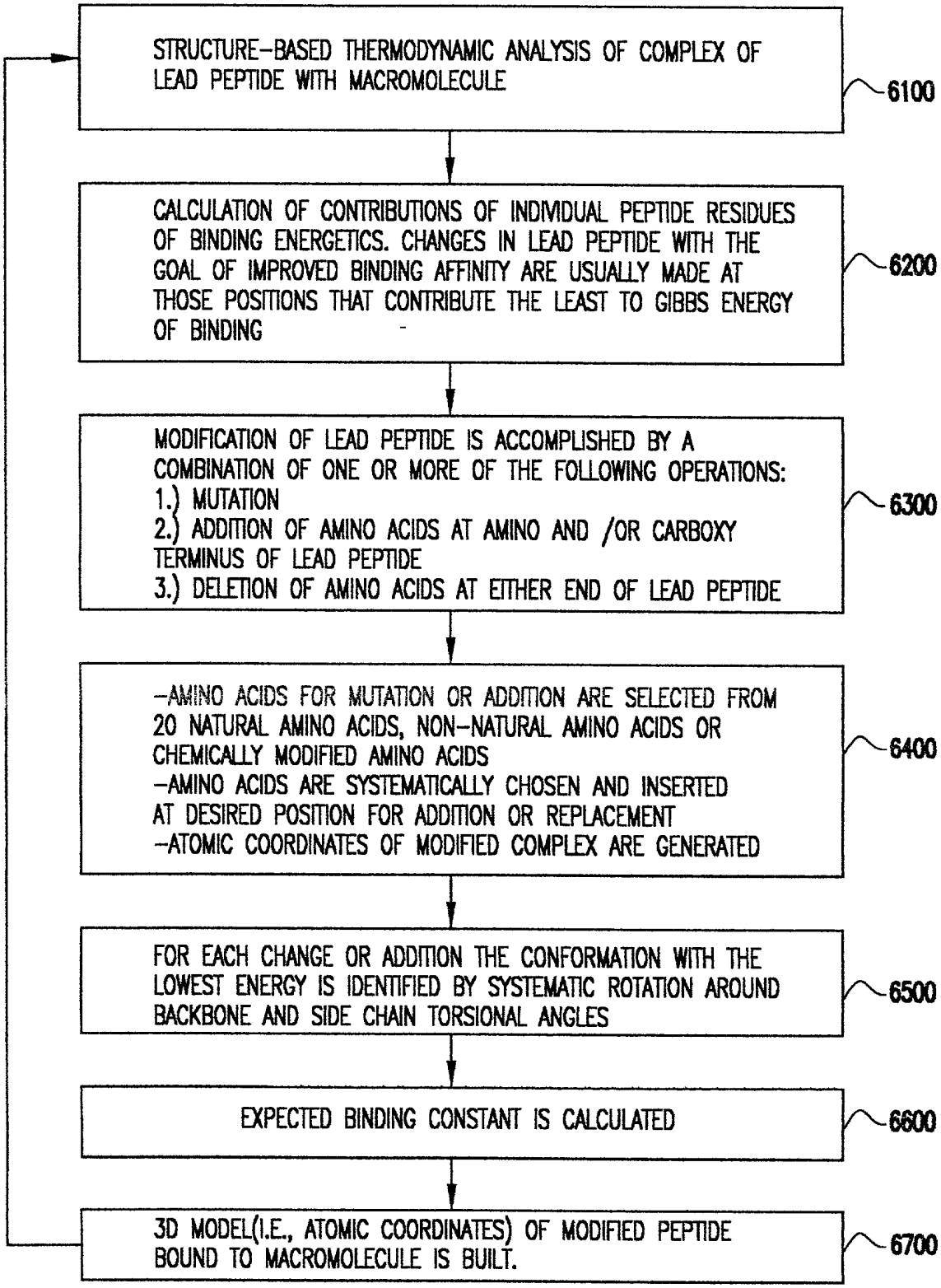

STRUCTURE-BASED THERMODYNAMIC ANALYSIS OF COMPLEX OF LEAD PEPTIDE WITH MACROMOLECULE
6100
CALCULATION OF CONTRIBUTIONS OF INDIVIDUAL PEPTIDE RESIDUES OF BINDING ENERGETICS. CHANGES IN LEAD PEPTIDE WITH THE GOAL OF IMPROVED BINDING AFFINITY ARE USUALLY MADE AT THOSE POSITIONS THAT CONTRIBUTE THE LEAST TO GIBBS ENERGY OF BINDING
6200
MODIFICATION OF LEAD PEPTIDE IS ACCOMPLISHED BY A COMBINATION OF ONE OR MORE OF THE FOLLOWING OPERATIONS:
1.) MUTATION
2.) ADDITION OF AMINO ACIDS AT AMINO AND /OR CARBOXY TERMINUS OF LEAD PEPTIDE
3.) DELETION OF AMINO ACIDS AT EITHER END OF LEAD PEPTIDE
6300
-AMINO ACIDS FOR MUTATION OR ADDITION ARE SELECTED FROM 20 NATURAL AMINO ACIDS, NON-NATURAL AMINO ACIDS OR CHEMICALLY MODIFIED AMINO ACIDS
-AMINO ACIDS ARE SYSTEMATICALLY CHOSEN AND INSERTED AT DESIRED POSITION FOR ADDITION OR REPLACEMENT
-ATOMIC COORDINATES OF MODIFIED COMPLEX ARE GENERATED
6400
FOR EACH CHANGE OR ADDITION THE CONFORMATION WITH THE LOWEST ENERGY IS IDENTIFIED BY SYSTEMATIC ROTATION AROUND BACKBONE AND SIDE CHAIN TORSIONAL ANGLES
6500
EXPECTED BINDING CONSTANT IS CALCULATED
6600
3D MODEL(I.E., ATOMIC COORDINATES) OF MODIFIED PEPTIDE BOUND TO MACROMOLECULE IS BUILT.
6700

FIG.5

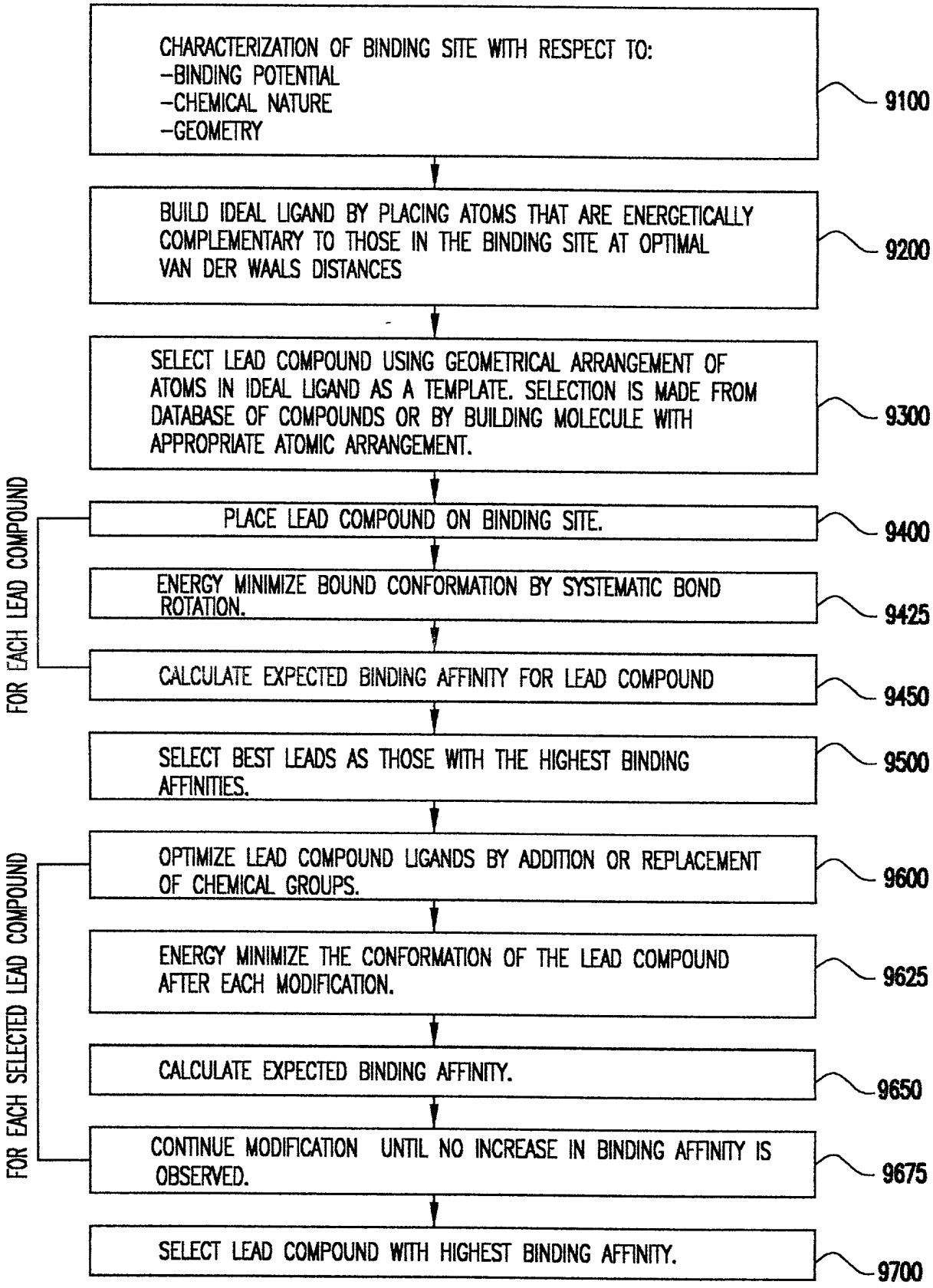

CHARACTERIZATION OF BINDING SITE WITH RESPECT TO:
-BINDING POTENTIAL
-CHEMICAL NATURE
-GEOMETRY
9100
BUILD IDEAL LIGAND BY PLACING ATOMS THAT ARE ENERGETICALLY COMPLEMENTARY TO THOSE IN THE BINDING SITE AT OPTIMAL VAN DER WAALS DISTANCES
9200
SELECT LEAD COMPOUND USING GEOMETRICAL ARRANGEMENT OF ATOMS IN IDEAL LIGAND AS A TEMPLATE. SELECTION IS MADE FROM DATABASE OF COMPOUNDS OR BY BUILDING MOLECULE WITH APPROPRIATE ATOMIC ARRANGEMENT.
9300
FOR EACH LEAD COMPOUND
PLACE LEAD COMPOUND ON BINDING SITE.
9400
ENERGY MINIMIZE BOUND CONFORMATION BY SYSTEMATIC BOND ROTATION.
9425
CALCULATE EXPECTED BINDING AFFINITY FOR LEAD COMPOUND
9450
SELECT BEST LEADS AS THOSE WITH THE HIGHEST BINDING AFFINITIES.
9500
FOR EACH SELECTED LEAD COMPOUND
OPTIMIZE LEAD COMPOUND LIGANDS BY ADDITION OR REPLACEMENT OF CHEMICAL GROUPS.
9600
ENERGY MINIMIZE THE CONFORMATION OF THE LEAD COMPOUND AFTER EACH MODIFICATION.
9625
CALCULATE EXPECTED BINDING AFFINITY.
9650
CONTINUE MODIFICATION UNTIL NO INCREASE IN BINDING AFFINITY IS OBSERVED.
9675
SELECT LEAD COMPOUND WITH HIGHEST BINDING AFFINITY.
9700

FIG.6

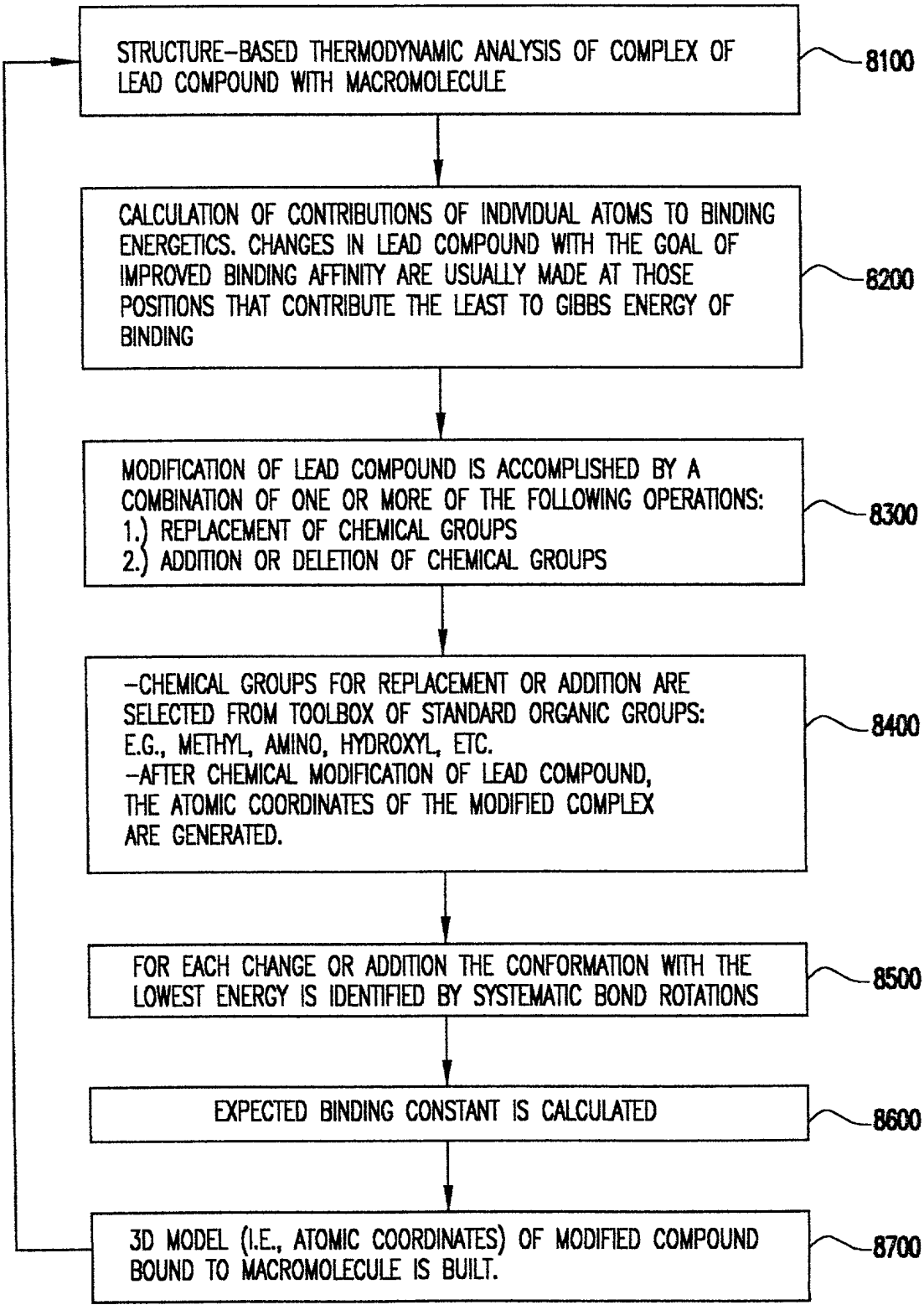

STRUCTURE-BASED THERMODYNAMIC ANALYSIS OF COMPLEX OF LEAD COMPOUND WITH MACROMOLECULE
8100
CALCULATION OF CONTRIBUTIONS OF INDIVIDUAL ATOMS TO BINDING ENERGETICS. CHANGES IN LEAD COMPOUND WITH THE GOAL OF IMPROVED BINDING AFFINITY ARE USUALLY MADE AT THOSE POSITIONS THAT CONTRIBUTE THE LEAST TO GIBBS ENERGY OF BINDING
8200
MODIFICATION OF LEAD COMPOUND IS ACCOMPLISHED BY A COMBINATION OF ONE OR MORE OF THE FOLLOWING OPERATIONS:
1.) REPLACEMENT OF CHEMICAL GROUPS
2.) ADDITION OR DELETION OF CHEMICAL GROUPS
8300
-CHEMICAL GROUPS FOR REPLACEMENT OR ADDITION ARE SELECTED FROM TOOLBOX OF STANDARD ORGANIC GROUPS: E.G., METHYL, AMINO, HYDROXYL, ETC.
-AFTER CHEMICAL MODIFICATION OF LEAD COMPOUND, THE ATOMIC COORDINATES OF THE MODIFIED COMPLEX ARE GENERATED.
8400
FOR EACH CHANGE OR ADDITION THE CONFORMATION WITH THE LOWEST ENERGY IS IDENTIFIED BY SYSTEMATIC BOND ROTATIONS
8500
EXPECTED BINDING CONSTANT IS CALCULATED
8600
3D MODEL (I.E., ATOMIC COORDINATES) OF MODIFIED COMPOUND BOUND TO MACROMOLECULE IS BUILT.
8700

FIG.7

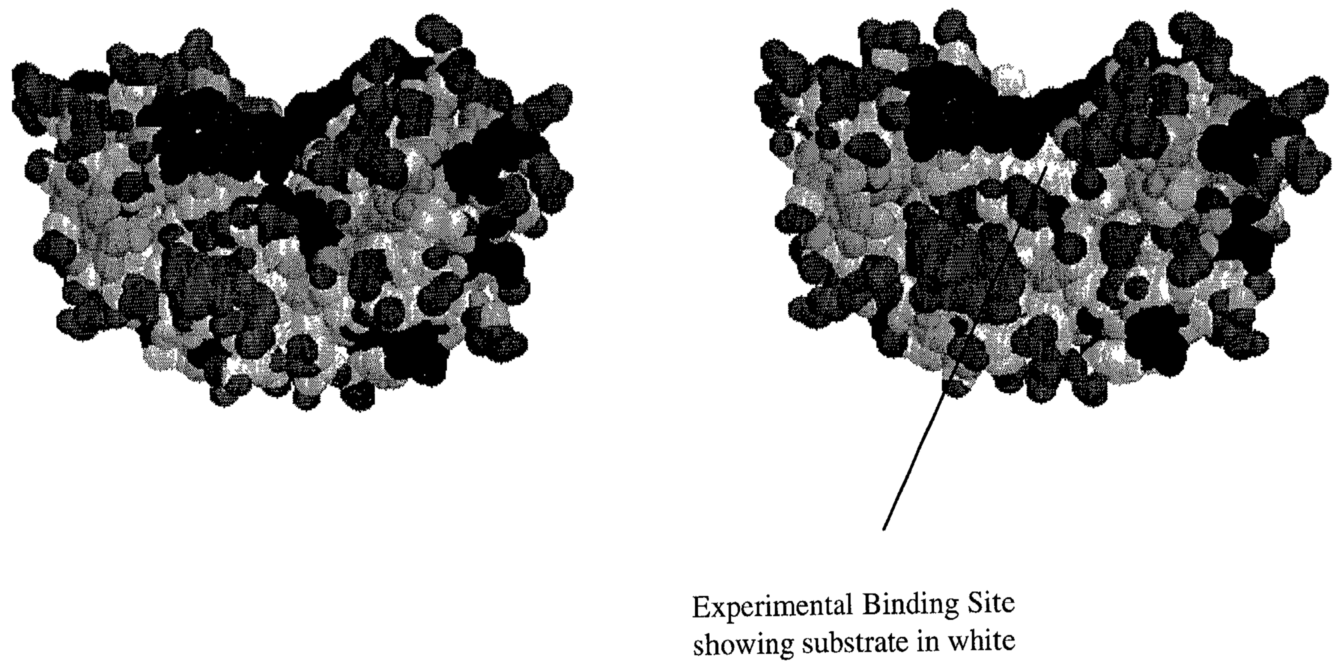
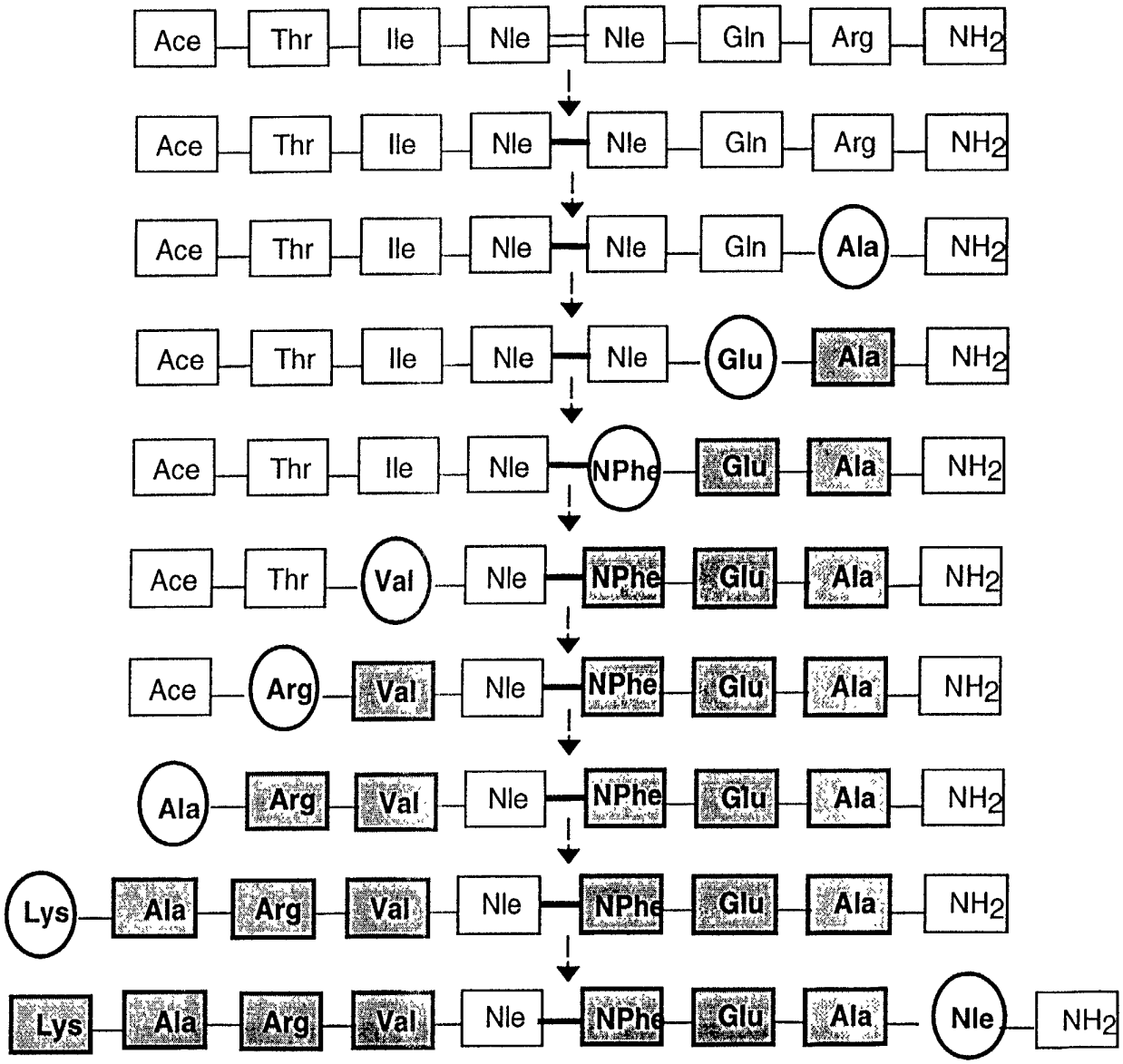
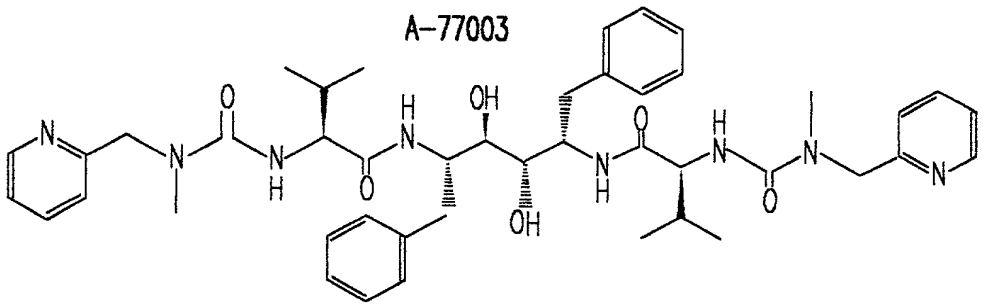


FIG.8

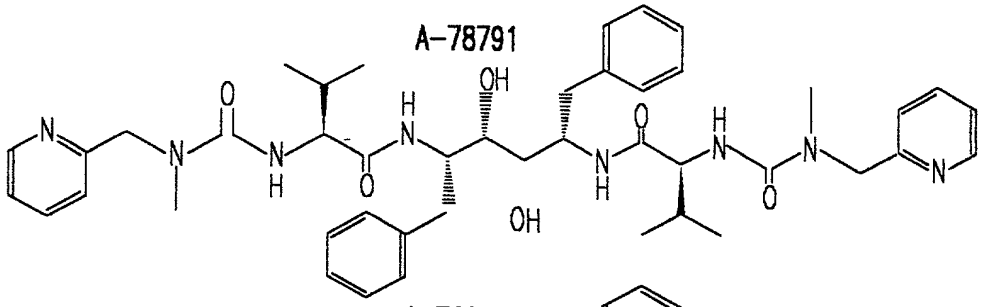
FIG.9



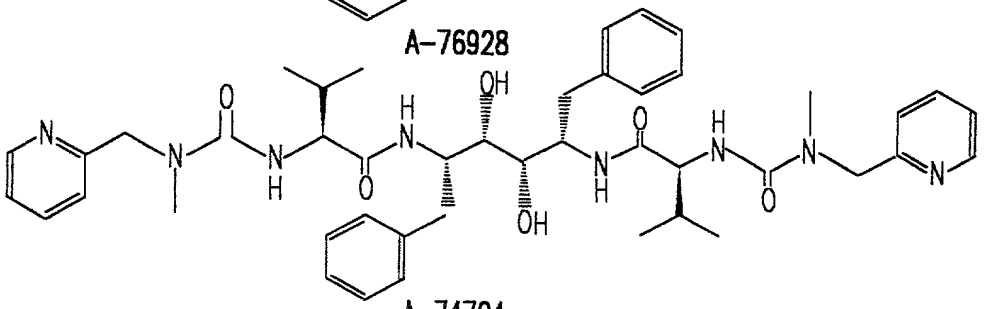
A-77003



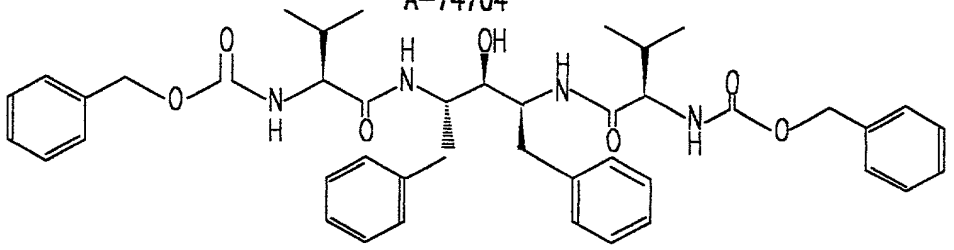
A-78791



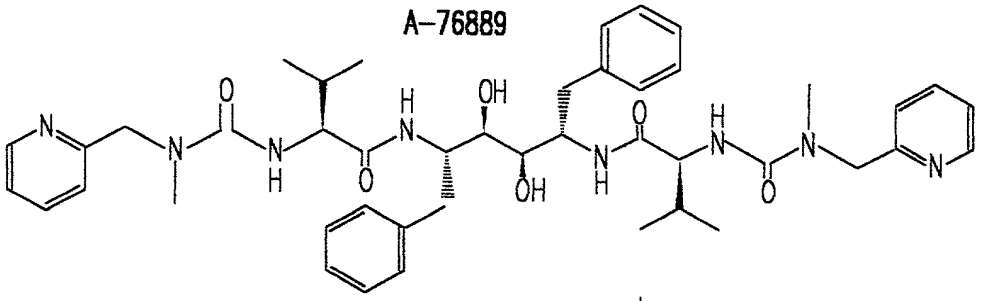
A-76928



A-74704



A-76889



VX478

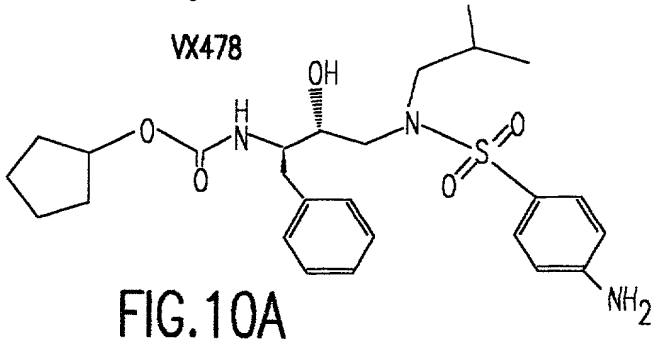
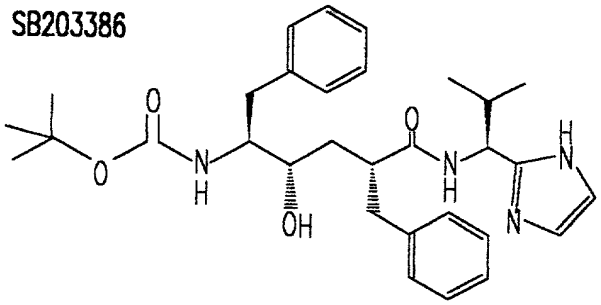
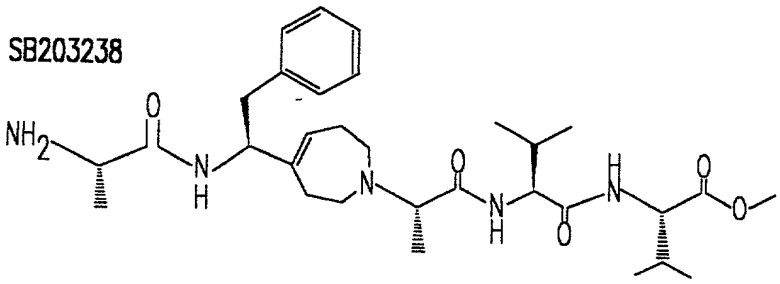


FIG.10A

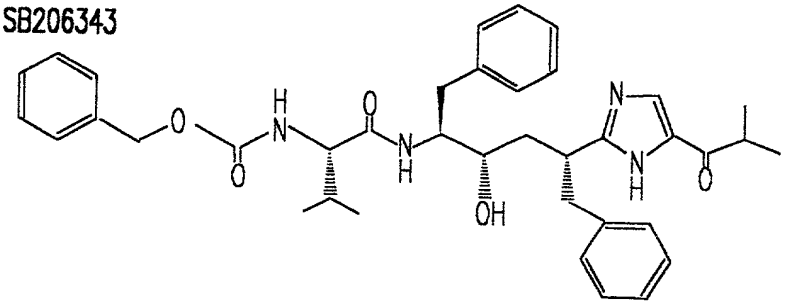
SB203386



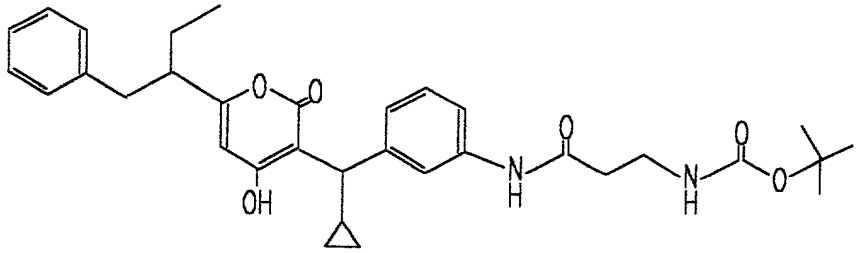
SB203238



SB206343



U100313



U-89360

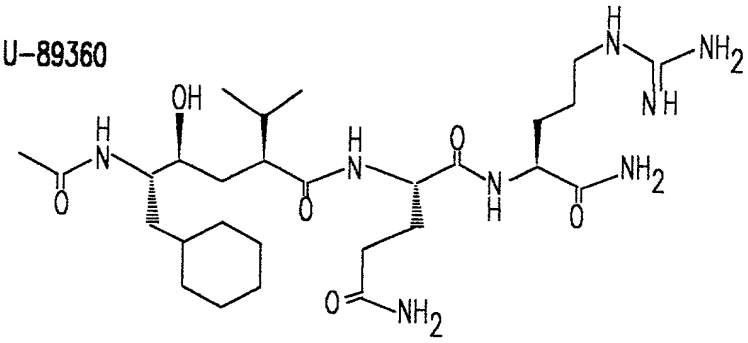
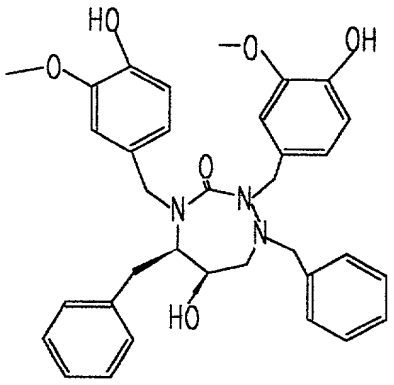


FIG.10B

A-98881



CGP 53820

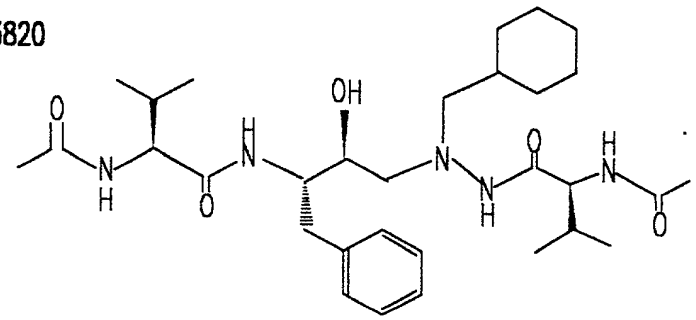


FIG.10C

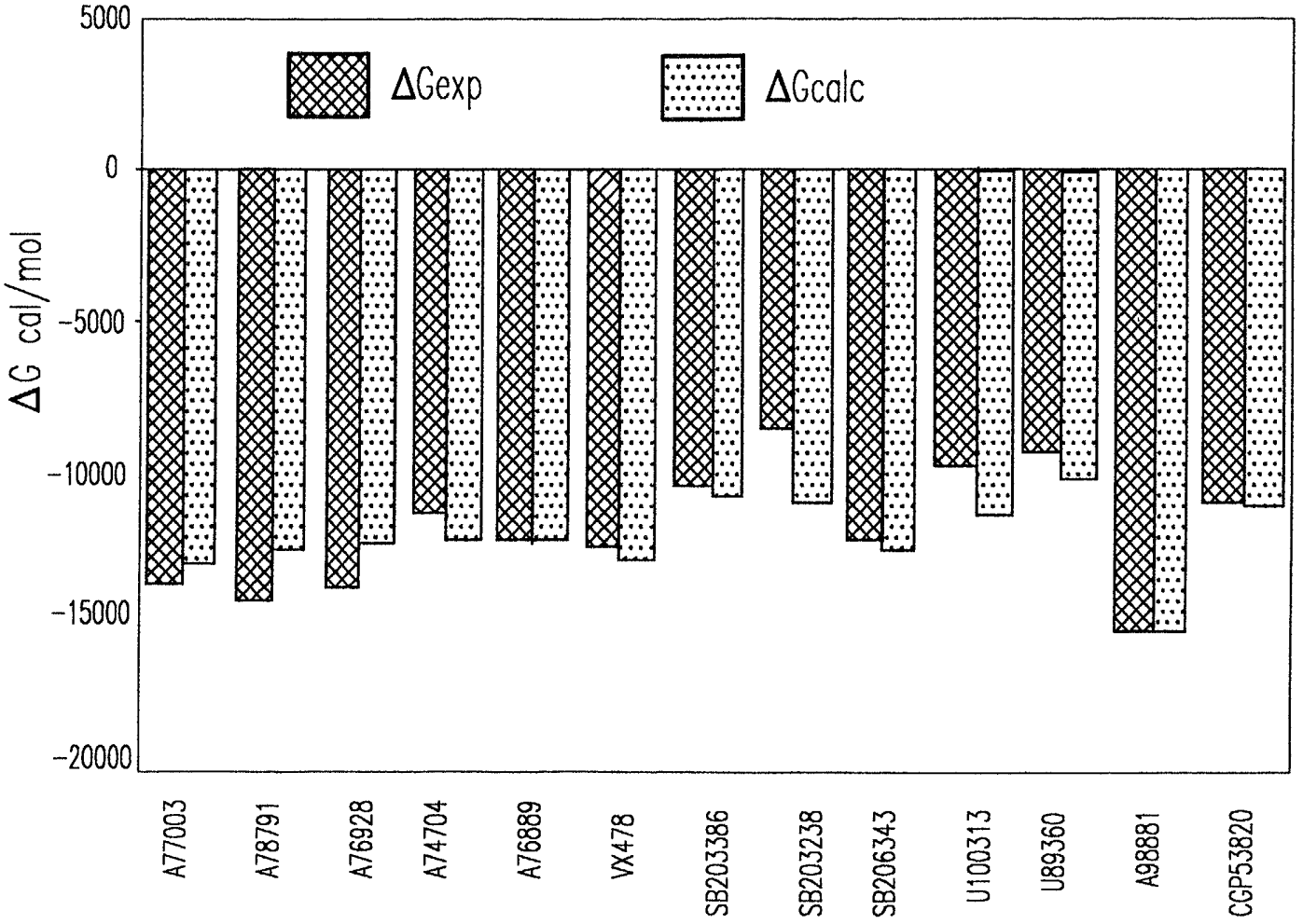


FIG.11

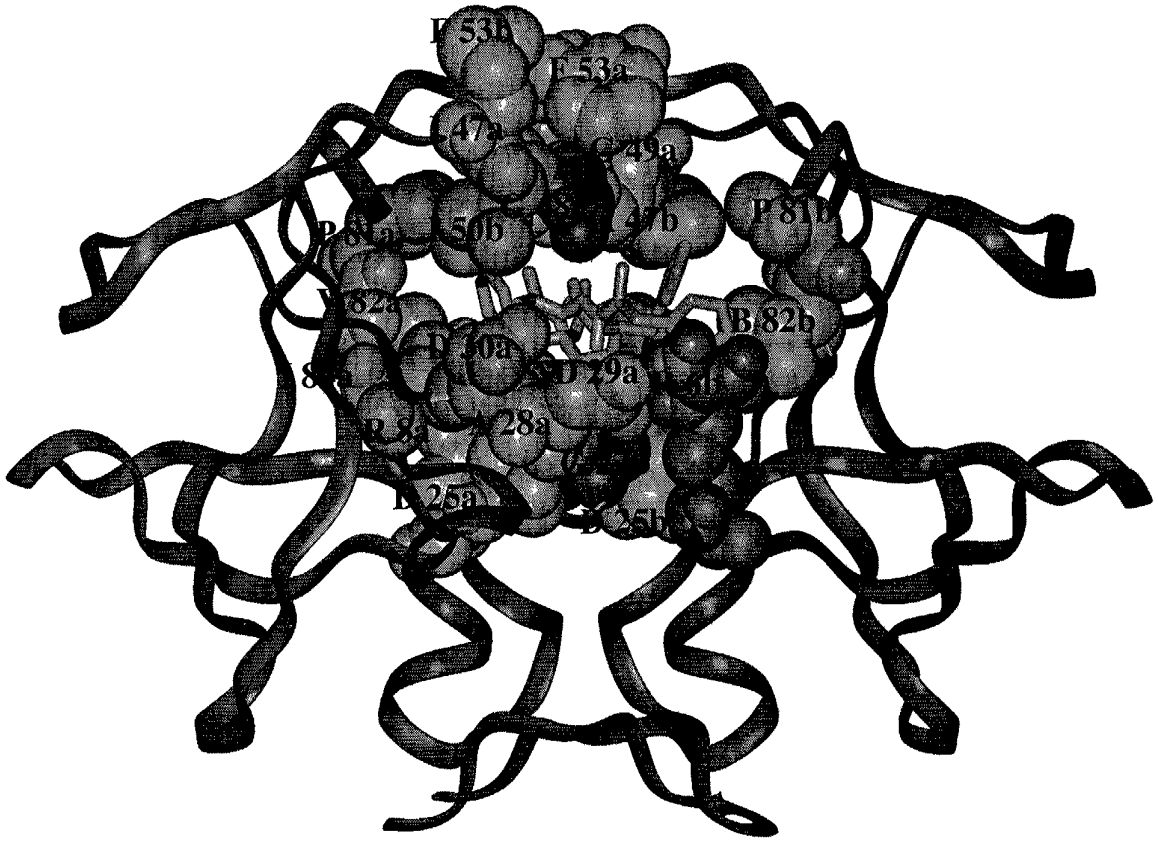


FIG.12A

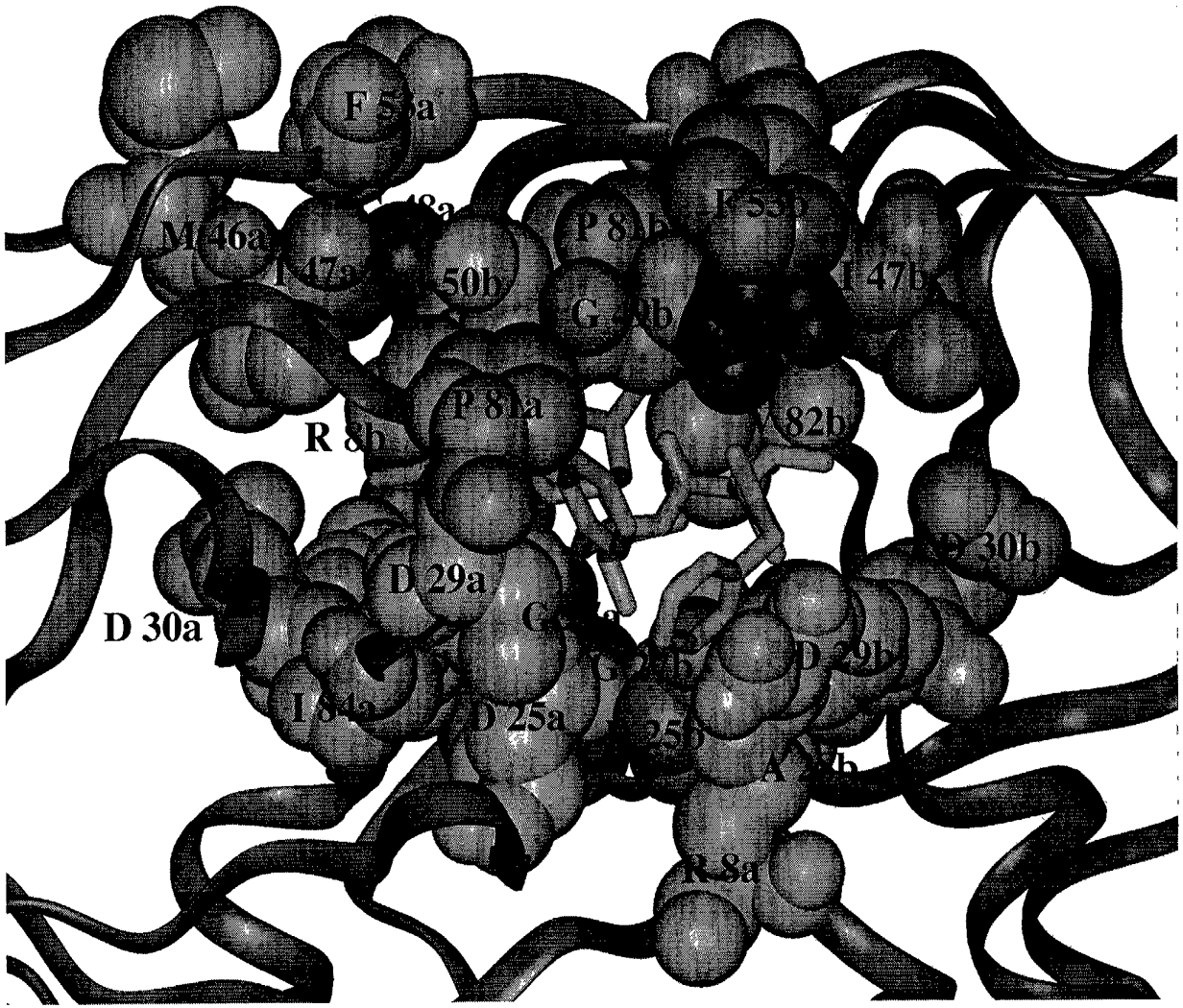


FIG. 12B

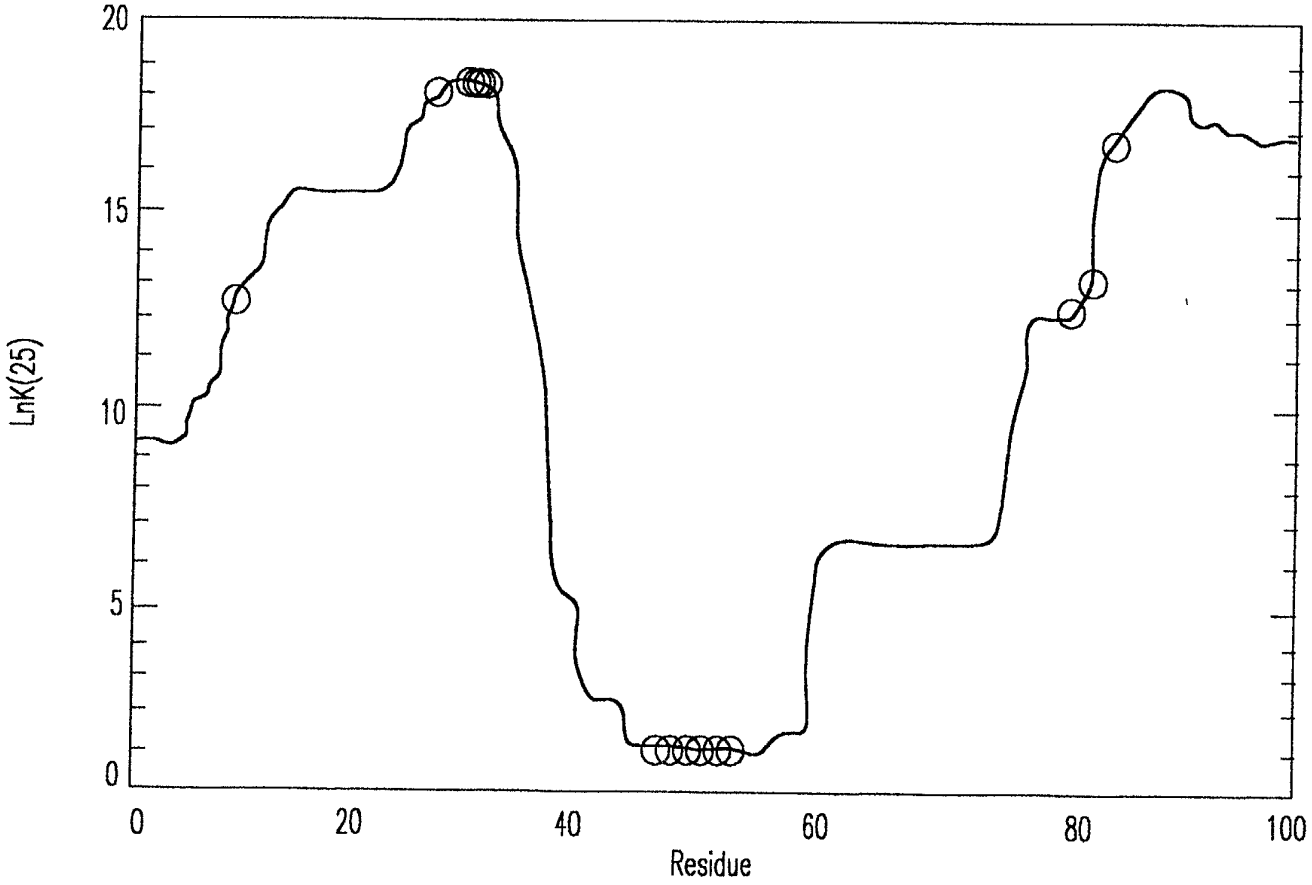


FIG.13

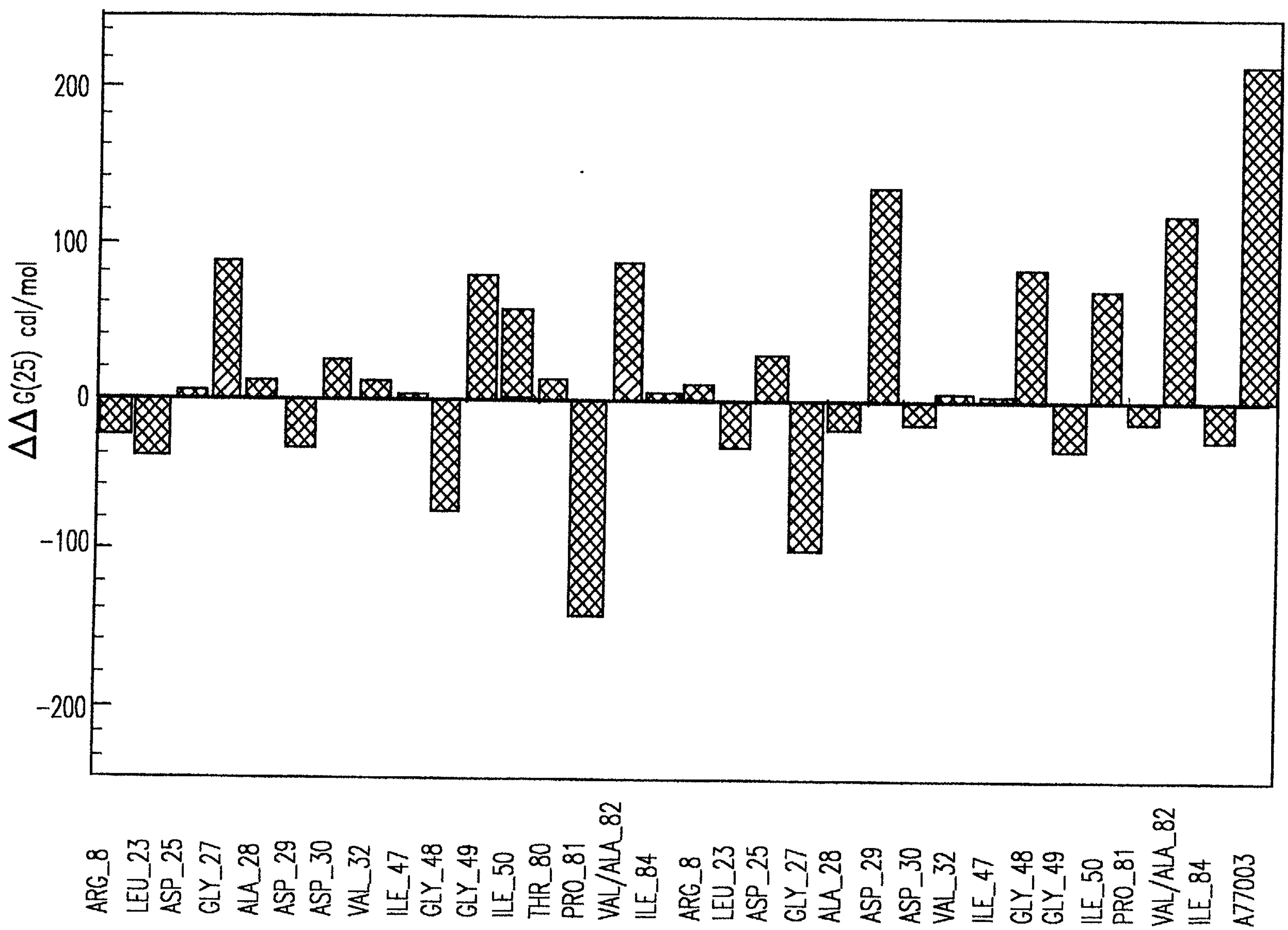


FIG.14

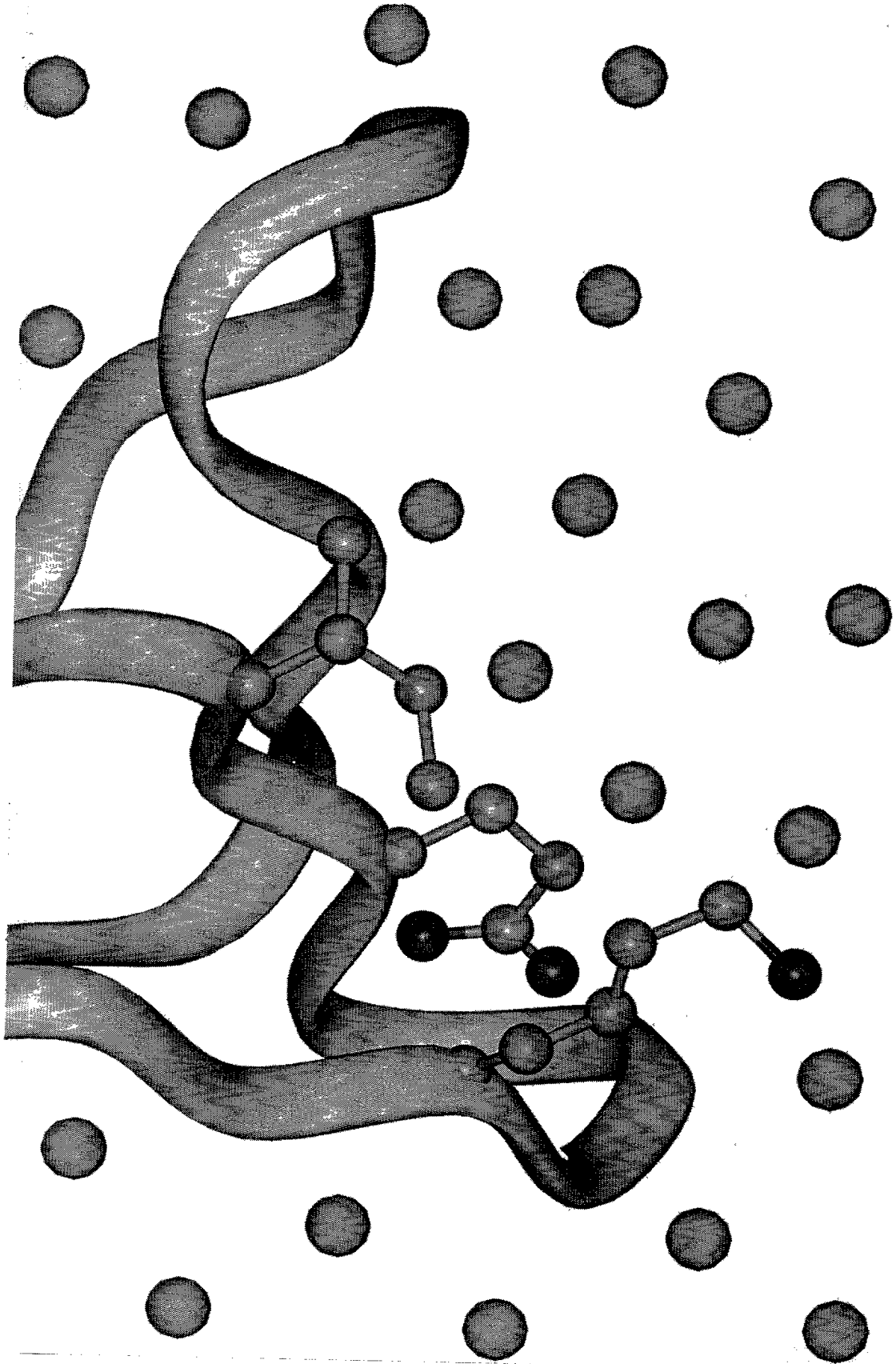


FIG. 15A

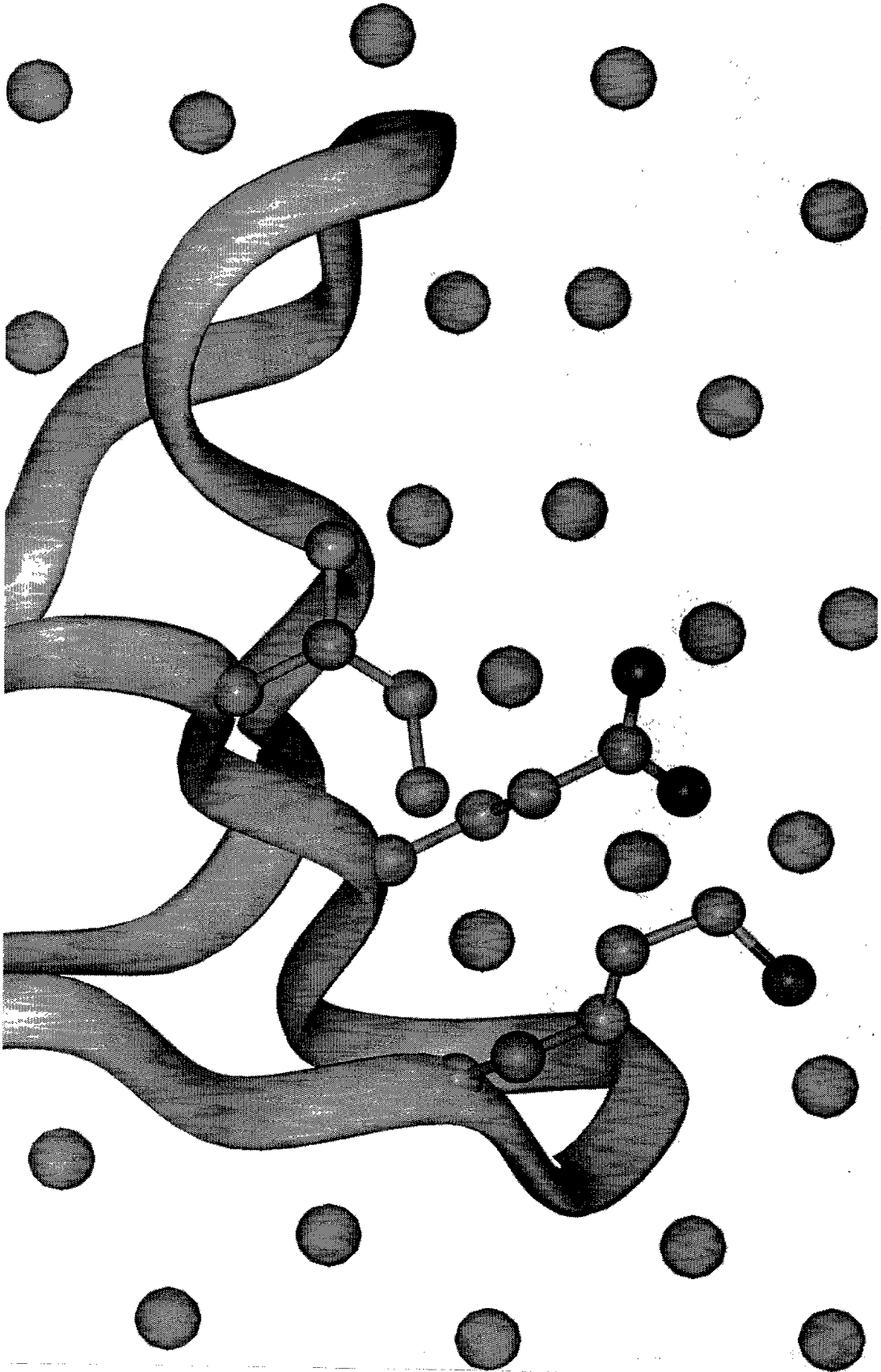


FIG.15B

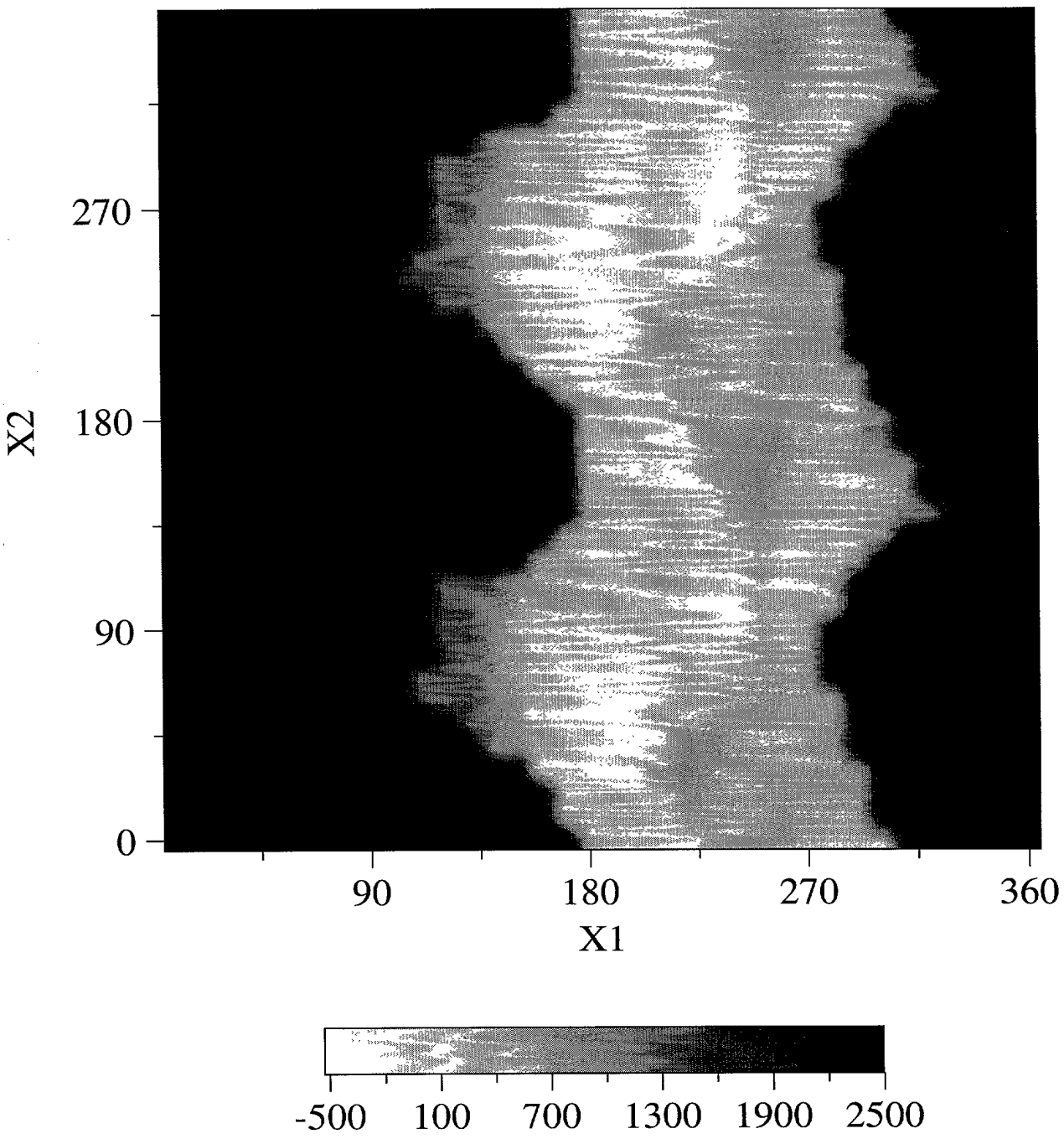


FIG.16

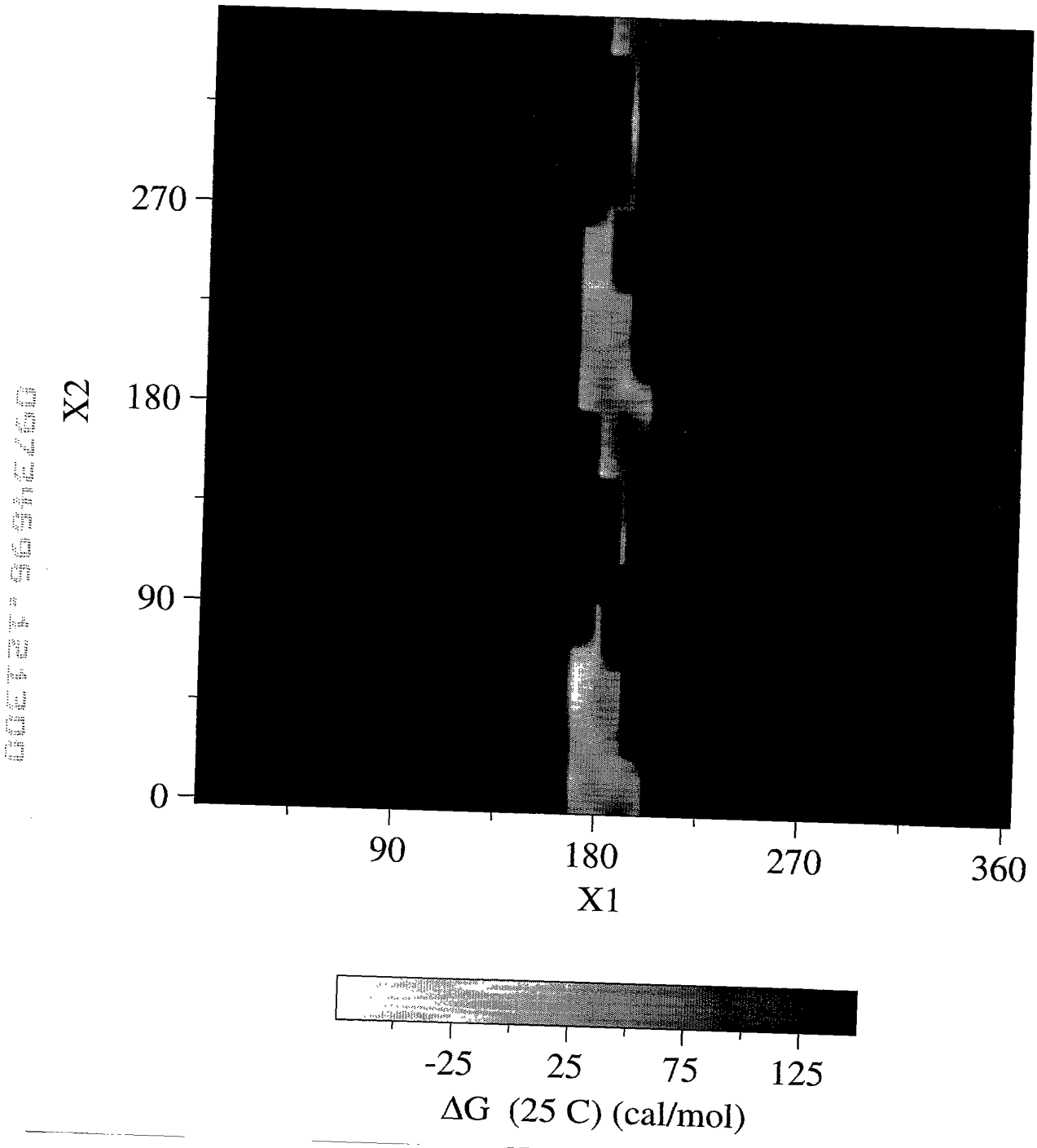


FIG.17

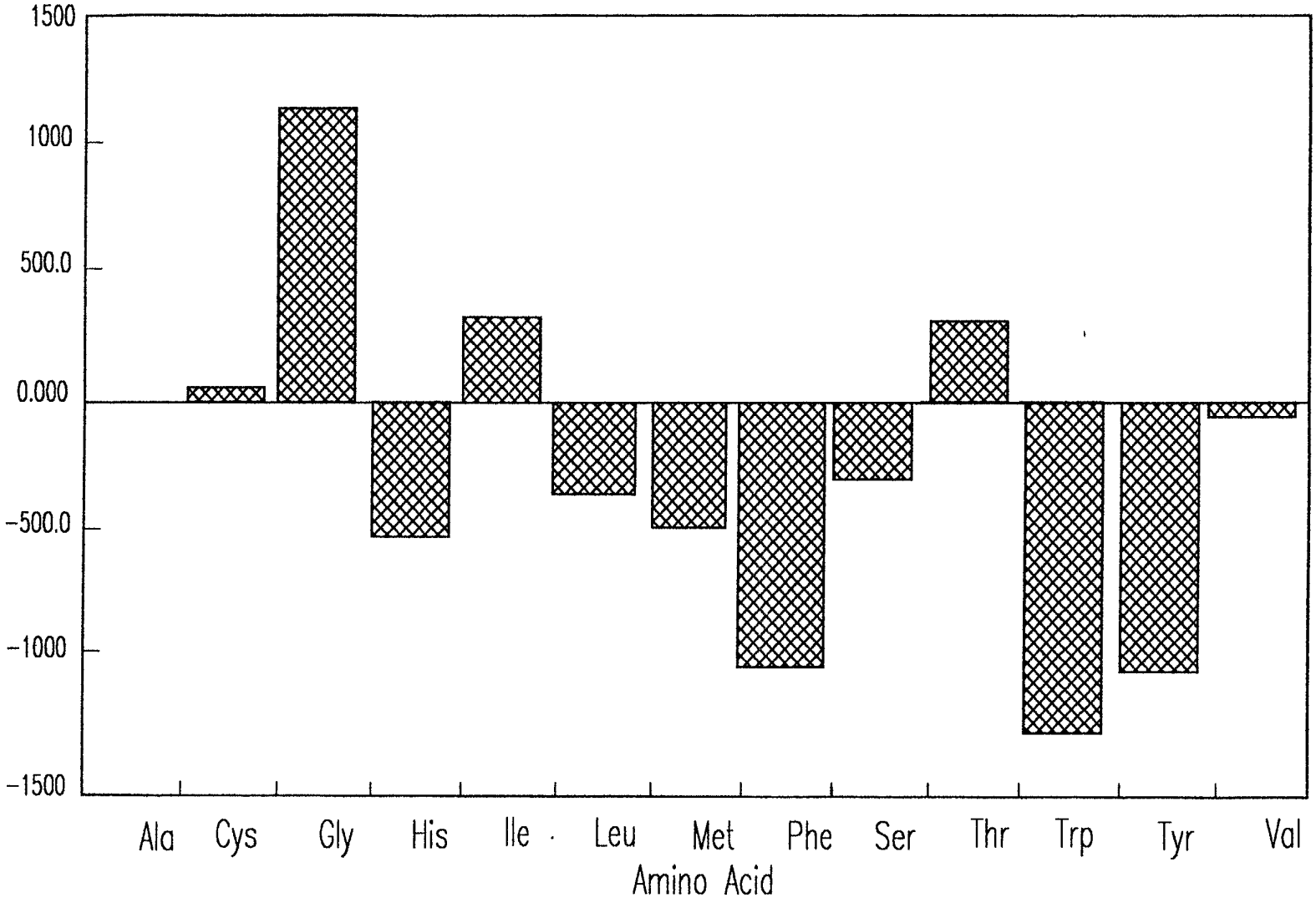


FIG.18

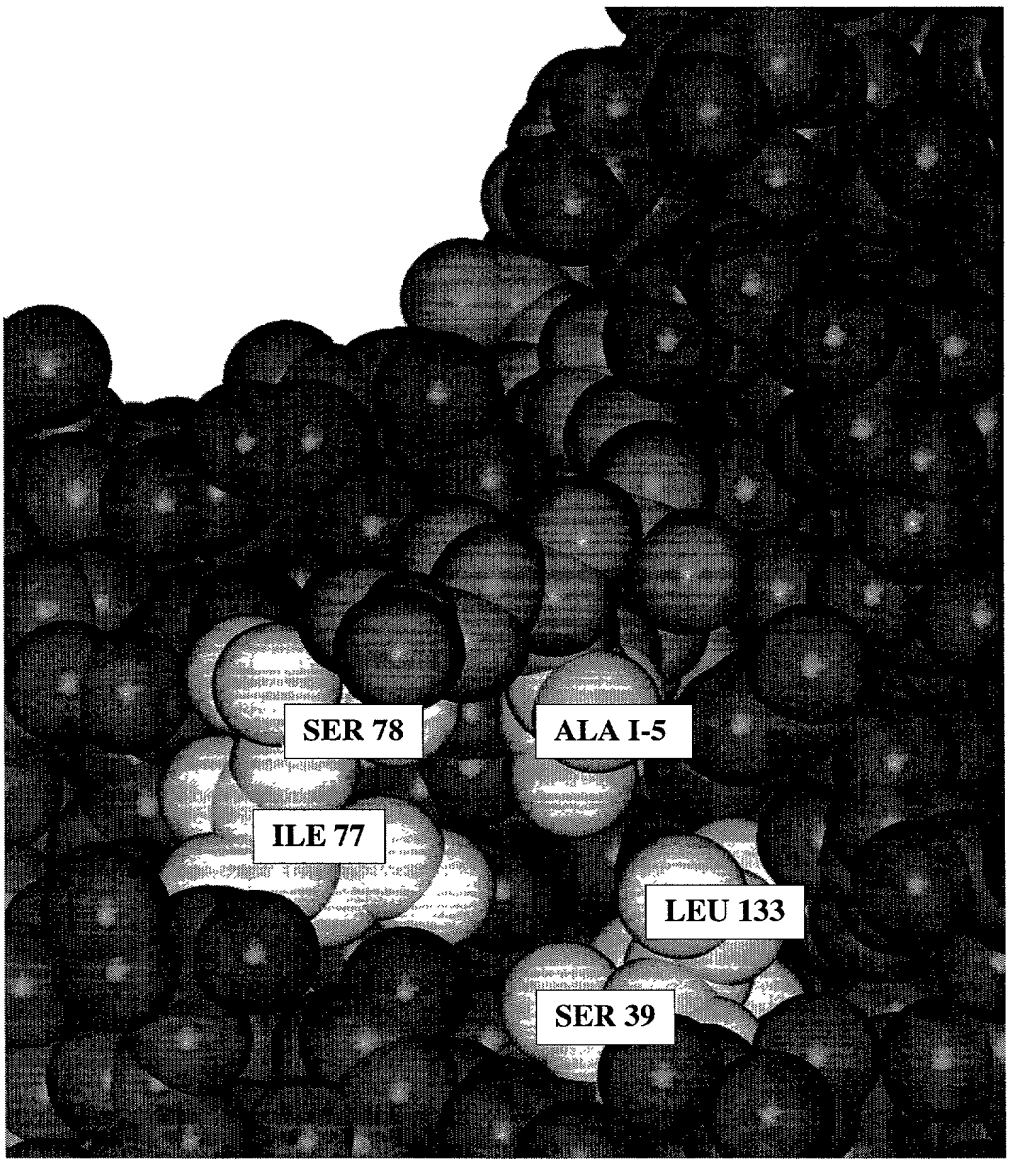


FIG. 19A

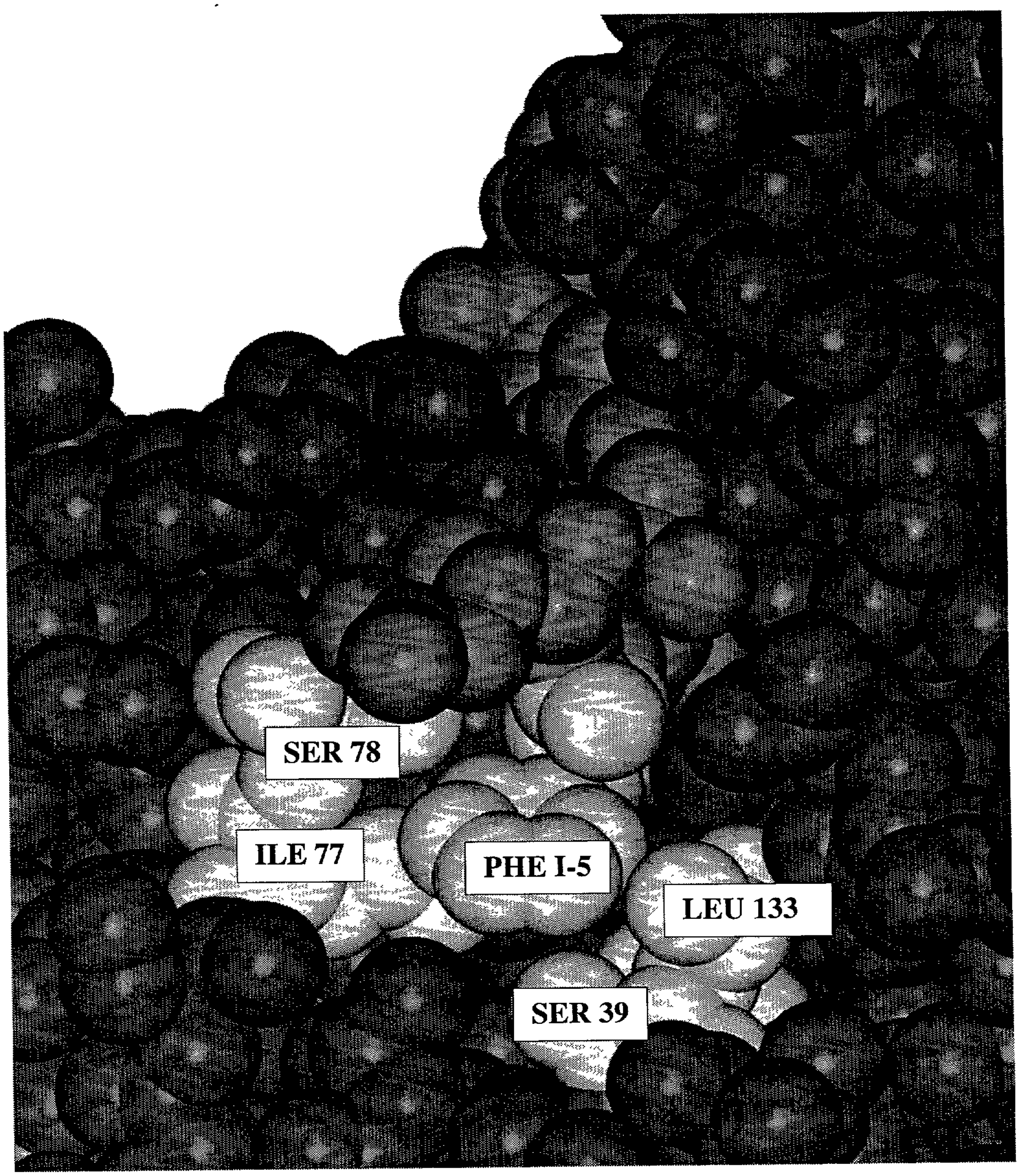


FIG.19B

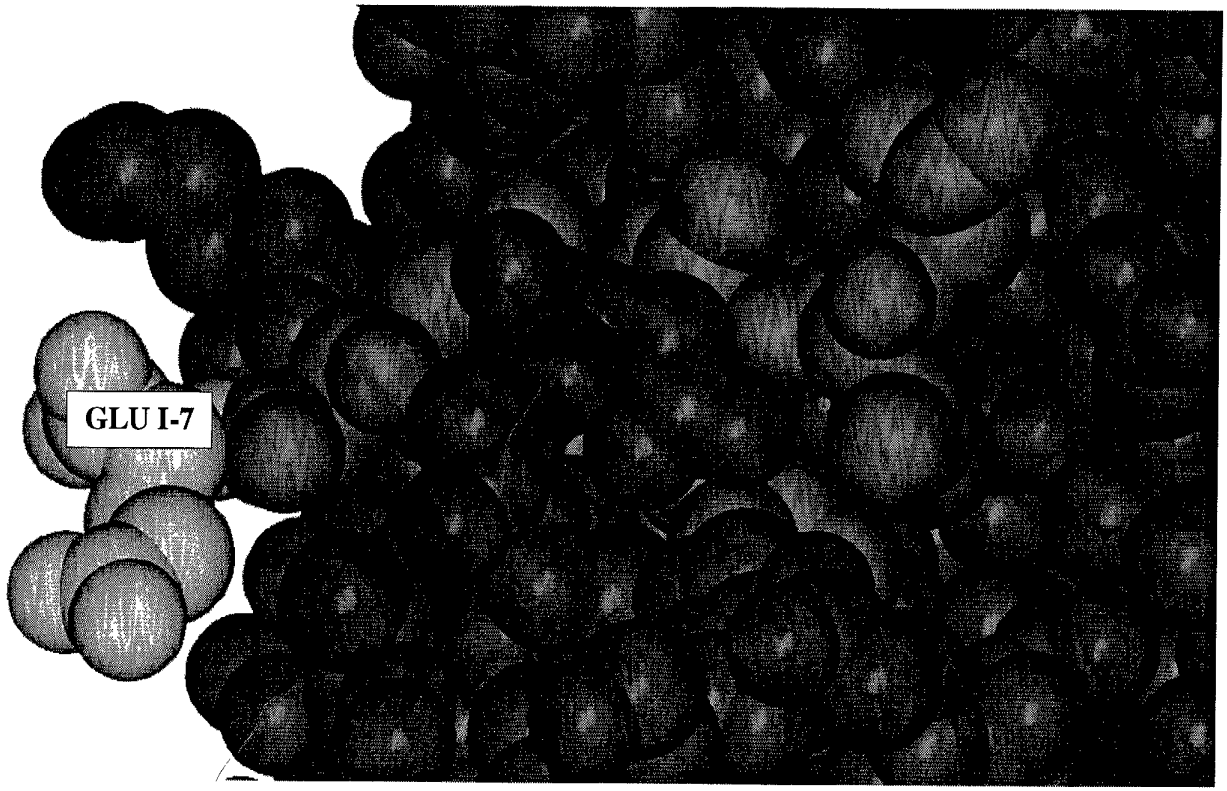


FIG.20